CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074123

Trade Name : PINDOLOL TABLETS USP 5MG AND 10MG

Generic Name: Pindolol Tablets USP 5mg and 10mg

Sponsor : Lemmon Company

Approval Date: April 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074123

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074123

APPROVAL LETTERS

ANDA 74-123

APR 17 1997

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Madam:

This is in reference to your abbreviated new drug application dated October 18, 1991, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Pindolol Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendments dated March 25, and April 30, 1992; April 7, 1993; and September 30, and November 15, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Pindolol Tablets USP, 5 mg and 10 mg, are bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Visken® Tablets, 5 mg and 10 mg, respectively, of Sandoz Pharmaceuticals Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drug
Center for Drug Evaluation and Research

4-17-97

CENTER FOR DRUG EVALUATION AND RESEARCH

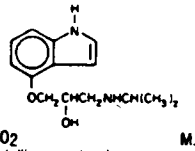
APPLICATION NUMBER 074123

FINAL PRINTED LABELING

PINDOLOL TABLETS, USP

DESCRIPTION

Pindolol, a synthetic beta-adrenergic receptor blocking agent with intrinsic sympathomimetic activity is 4-(2-hydroxy-3-isopropylaminopropoxy)-indole.



$C_{14}H_{20}N_2O_2$ M. W. 248.32

Pindolol is a white to off-white, crystalline powder, having a faint odor. Practically insoluble in water; slightly soluble in methanol; very slightly soluble in chloroform.

5 mg and 10 mg Tablets

Active Ingredient: pindolol

Inactive Ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

CLINICAL PHARMACOLOGY

Pindolol is a non-selective beta-adrenergic antagonist (beta-blocker) which possesses intrinsic sympathomimetic activity (ISA) in therapeutic dosage ranges but does not possess quinidine-like membrane stabilizing activity.

PHARMACODYNAMICS

In standard pharmacologic tests in man and animals, pindolol attenuates increases in heart rate, systolic blood pressure and cardiac output resulting from exercise and isoproterenol administration, thus confirming its beta-blocking properties. The ISA or partial agonist activity of pindolol is mediated directly at the adrenergic receptor sites and may be blocked by other beta-blockers. In catecholamine depleted animal experiments, ISA is manifested as an increase in the inotropic and chronotropic activity of the myocardium. In man, ISA is manifested by a smaller reduction in the resting heart rate (4-8 beats/min) than is seen with drugs lacking ISA. There is also a smaller reduction in resting cardiac output. The clinical significance of this observation has not been evaluated and there is no evidence, or reason to believe, that exercise cardiac output is less affected by pindolol.

Pindolol has been shown in controlled, double-blind clinical studies to be an effective antihypertensive agent when used as monotherapy, or when added to therapy with thiazide-type diuretics. Divided dosages in the range of 10-60 mg daily have been shown to be effective. As monotherapy, pindolol is as effective as propranolol, α-methyldopa, hydrochlorothiazide and chlorthalidone in reducing systolic and diastolic blood pressure. The effect on blood pressure is not orthostatic, i.e. pindolol was equally effective in reducing the supine and standing blood pressure.

In open, long-term studies up to four (4) years, no evidence of diminution of the blood pressure lowering response was observed.

An average 3 pound increase in body weight has been noted in patients treated with pindolol alone, a larger increase than was observed with propranolol or placebo. The weight gain appeared unrelated to blood pressure response and was not associated with an increased risk of heart failure, although edema was more common than in control patients. Pindolol does not have a consistent effect on plasma renin activity.

The mechanism of the antihypertensive effects of beta-blocking agents has not been established, but several mechanisms have been postulated: 1) an effect on the central nervous system resulting in a reduced sympathetic outflow to the periphery, 2) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic receptor sites, leading to decreased cardiac output, 3) an inhibition of renin release. These mechanisms appear less likely for pindolol than other beta-blockers in view of the modest effect on resting cardiac output and renin.

Beta-blockade therapy is useful when it is necessary to suppress the effects of beta-adrenergic agonists in order to achieve therapeutic goals. However, in certain clinical situations, (e.g., cardiac failure, heart block, bronchospasm), the preservation of an adequate sympathetic tone may be necessary to maintain vital functions. Although a beta-antagonist with ISA such as pindolol does not eliminate sympathetic tone entirely, there is no controlled evidence that it is safer than other beta-blockers in such conditions as heart failure, heart block, or bronchospasm or is less likely to cause those conditions. In single dose studies of the effects of beta-blockers on FEV_1, pindolol was indistinguishable from other non-cardioselective agents in its reduction of FEV_1, and its reduction in the effectiveness of an exogenous beta agonist.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmias have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

PHARMACOKINETICS AND METABOLISM

Pindolol is rapidly and reproducibly absorbed (greater than 95%), achieving peak plasma concentrations within 1 hour of drug administration. Pindolol has no significant first-pass effect. The blood concentrations are proportional in a linear manner to the administered dose in the range of 5-20 mg. Upon repeated administration to the same subject, variation is minimal. After a single dose, intersubject variation for peak plasma concentrations was about 4 fold for a 20 mg dose. Upon multiple dosing, intersubject variation decreased to 2-2.5 fold. Pindolol is only 40% bound to plasma proteins and is evenly distributed between plasma and red cells. The volume of distribution in healthy subjects is about 2 L/kg.

Pindolol undergoes extensive metabolism in animals and man. In man, 35-40% is excreted unchanged in the urine and 60-65% is metabolized primarily to hydroxy-metabolites which are excreted as glucuronides and ethereal sulfates. The polar metabolites are excreted with a half-life of approximately 8 hours and thus multiple dosing therapy (q. 8H) results in a less than 50% accumulation in plasma. About 6-9% of an administered intravenous dose is excreted by the bile into the feces.

The disposition of pindolol after oral administration is monophasic with a half-life in healthy subjects or hypertensive patients with normal renal function of approximately 3-4 hours. Following t.i.d. administration (q. 8H), no significant accumulation of pindolol is observed.

In elderly hypertensive patients with normal renal function, the half-life of pindolol is more variable, averaging about 7 hours, but with values as high as 15 hours.

In hypertensive patients with renal diseases, the half-life is within the range expected for healthy subjects. However, a significant decrease (50%) in volume of distribution (V_D) is observed in uremic patients and V_D appears to be directly correlated to creatinine clearance. Therefore, renal drug clearance is significantly reduced in uremic patients, resulting in a significant decrease in urinary excretion of unchanged drug. Uremic patients with a creatinine clearance of less than 20 mL/min generally excreted less than 15% of the administered dose unchanged in the urine.

In patients with histologically diagnosed cirrhosis of the liver, the elimination of pindolol was more variable in rate and generally significantly slower than in healthy subjects. The total body clearance of pindolol in cirrhotic patients ranged from about 50-300 mL/min and was directly correlated to antipyrine clearance. The half-life ranges from 2.5 hours to greater than 30 hours. These findings strongly suggest that caution should be exercised in dosage adjustments of pindolol in such patients.

The bioavailability of pindolol is not significantly affected by co-administration of food, hydralazine, hydrochlorothiazide or aspirin. Pindolol has no effect on warfarin activity or the clinical effectiveness of digoxin, although small transient decreases in plasma digoxin concentrations were noted.

INDICATIONS AND USAGE

Pindolol tablets are indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS

Pindolol tablets are contraindicated [illegible]

concentrations are proportional in a linear manner to the administered dose in the range of 5-20 mg. Upon repeated administration to the same subject, variation is minimal. After a single dose, intersubject variation for peak plasma concentrations was about 4 fold for a 20 mg dose. Upon multiple dosing, intersubject variation decreased to 2-2.5 fold. Pindolol is only 40% bound to plasma proteins and is evenly distributed between plasma and red cells. The volume of distribution in healthy subjects is about 2 L/kg.

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INDICATIONS AND USAGE

Pindolol tablets are indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS

Pindolol tablets are contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia. (*See WARNINGS.*)

WARNINGS

Cardiac Failure - Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, pindolol can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure - In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, pindolol therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal - Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered pindolol particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, pindolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue pindolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) - Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers - Pindolol should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery - Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be gradually withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy.

The effects of pindolol can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia - Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis - Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS

Impaired Renal or Hepatic Function - Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on pindolol clearance, but poor hepatic function may cause blood levels of pindolol to increase substantially.

Information for Patients - Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of pindolol therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions - Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving pindolol plus a catecholamine-depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Pindolol has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Pindolol has been shown to increase serum thioridazine levels when both drugs are coadministered. Pindolol levels may also be increased with this combination.

Risk of anaphylactic reaction: While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility - In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, pindolol did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, pindolol did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, pindolol caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was asssociated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered pindolol as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered pindolol prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy - Category B - Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, pindolol, as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - Since pindolol is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use - Safety and effectiveness in children have not been established.

CLINICAL LABORATORY

Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during pindolol administration, but progressive elevations were not observed. These elevations were not associated with any other abnormalities that would suggest hepatic impairment, such as decreased serum albumin and total proteins. During more than a decade of worldwide marketing, there have been no reports in the medical literature of overt hepatic injury. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS

Most adverse reactions have been mild. The incidences listed in the following table are derived from 12-week comparative double-blind, parallel design trials in hypertensive patients given pindolol as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for pindolol and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. When considering all adverse reactions reported, the frequency of edema was noticeably higher in positive control trials (16% pindolol vs. 9% positive control) than in placebo controlled trials (6% pindolol vs. 3% placebo). The table includes adverse reactions either volunteered or elicited, and at least possibly drug related, which were reported in greater than 2% of pindolol patients and other selected important reactions.

Adverse Reactions which were Volunteered or Elicited (and at least possibly drug related)

Body System/ Adverse Reactions	Pindolol (N=322) %	Active Controls* (N=188) %	Placebo (N=78) %
Central Nervous System			
Bizarre or Many Dreams	5	0	6
Dizziness	9	11	1
Fatigue	8	4	4
Hallucinations	<1	0	0
Insomnia	10	3	10
Nervousness	7	3	5
Weakness	4	2	1
Autonomic Nervous System			
Paresthesia	3	1	6
Cardiovascular			
Dyspnea	5	4	6
Edema	6	3	1
Heart Failure	<1	<1	0
Palpitations	<1	1	0
Musculoskeletal			
Chest Pain	3	1	3
Joint Pain	7	4	4
Muscle Cramps	3	1	0
Muscle Pain	10	9	8
Gastrointestinal			
Abdominal Discomfort	4	4	5
Nausea	5	2	1
Skin			
Pruritus	1	<1	0
Rash	<1	<1	1

*Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to pindolol is uncertain. CENTRAL NERVOUS SYSTEM: anxiety, lethargy; AUTONOMIC NERVOUS SYSTEM: visual disturbances, hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia, weight gain; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS

In addition, other adverse effects not aforementioned have been reported with other beta-adrenergic

Cardiovascular			
Dyspnea	5	4	6
Edema	6	3	1
Heart Failure	<1	<1	0
Palpitations	<1	1	0
Musculoskeletal			
Chest Pain	3	1	3
Joint Pain	7	4	4
Muscle Cramps	3	1	0
Muscle Pain	10	9	8
Gastrointestinal			
Abdominal Discomfort	4	4	5
Nausea	5	2	1
Skin			
Pruritus	1	<1	0
Rash	<1	<1	1

*Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

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POTENTIAL ADVERSE EFFECTS

In addition, other adverse effects not aforementioned have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of pindolol.

Central Nervous System - Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular - Intensification of AV block. *(See CONTRAINDICATIONS)*

Allergic - Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic - Agranulocytosis; thrombocytopenic and nonthrombocytopenic purpura.

Gastrointestinal - Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous - Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with pindolol during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE

No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of pindolol, the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia - Administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure - Digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension - Administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm - Administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of pindolol by a hypertensive patient. Blood pressure increased and heart rate was ≥ 80 beat/min. Recovery was uneventful. In another case, 250 mg of pindolol was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION

The dosage of pindolol should be individualized. The recommended initial dose of pindolol is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

HOW SUPPLIED

Pindolol is provided as follows:

The 5 mg tablets are white, round, scored and engraved "93"-"678". Available in bottles of 100 and 1000.

The 10 mg tablets are white, round, scored and engraved "93"-"679". Available in bottles of 100 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION: Federal law prohibits dispensing without prescription.

Printed in USA
Rev. B 1/93
117612

Manufactured by:
LEMMON COMPANY
Sellersville, PA 18960

NDC 0093-0678-01

PINDOLOL
Tablets, USP
5 mg

Each tablet contains:
Pindolol, USP 5 mg

Caution: Federal law prohibits dispensing without prescription.

LEMMON

Usual Adult Dosage: One tablet twice daily. See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
This is a bulk package. Dispense contents in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN

L17610 IH Iss. 9/91

LEMMON COMPANY
Sellersville, PA 18960

N 0093-0678-01

NDC 0093-0679-01

PINDOLOL
Tablets, USP
10 mg

Each tablet contains:
Pindolol, USP 10 mg

Caution: Federal law prohibits dispensing without prescription.

100 TABLETS

LEMMON

Usual Adult Dosage: One tablet twice daily. See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
This is a bulk package. Dispense contents in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN

L17613 IH Iss. 9/91

LEMMON COMPANY Sellersville, PA 18960

N 0093-0679-01

NDC 0093-0678-10

PINDOLOL
Tablets, USP
5 mg

Each tablet contains:
Pindolol, USP 5 mg

Caution: Federal law prohibits dispensing without prescription.

1000 TABLETS

LEMMON

Usual Adult Dosage: One tablet twice daily. See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
This is a bulk package. Dispense contents in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN

L17611 IH Iss. 9/91

LEMMON COMPANY
Sellersville, PA 18960

N 0093-0678-10

NDC 0093-0679-10

PINDOLOL
Tablets, USP
10 mg

Each tablet contains:
Pindolol, USP 10 mg

Caution: Federal law prohibits dispensing without prescription.

1000 TABLETS

LEMMON

Usual Adult Dosage: One tablet twice daily. See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
This is a bulk package. Dispense contents in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN

L17614 IH Iss. 9/91

LEMMON COMPANY
Sellersville, PA 18960

N 0093-0679-10

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074123

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4

2. ANDA #74-123

3. NAME AND ADDRESS OF APPLICANT
Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960
Telephone: (215) 723-5544

4. LEGAL BASIS FOR SUBMISSION
Visken Tablets - Sandoz Pharmaceuticals Corporation
No patents or exclutivities in force.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Pindolol Tablets USP.

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

FIRM:

October 18, 1991:	Original submission.
March 25, 1992:	Bio. correspond.
March 27, 1992:	Correspond to FDA letter dated 3-5-92.
April 30, 1992:	Bio.correspond.
May 13, 1992:	Amendment.
April 7, 1993:	Labeling amendment.
March 24, 1994:	Minor amendment.
April 25, 1994:	Telephone amendment.
September 30, 1996:	Minor amendment.
November 15, 1996:	Telephone amendment.

FDA:

November 26, 1991:	Acknowledgement letter.
March 5, 1992:	NA letter.
August 24, 1992:	NA letter.
December 9,1992:	Labeling letter.
April 13, 1994:	Telephone conversation.
November 8, 1994:	FDA's Cincinati Dis. Off.letter
November 30, 1994:	CGMP deficiency letter.
November 1, 1996:	Telephone conversation

10. PHARMACOLOGICAL CATEGORY
Vasodilator

11. Rx or OTC
Rx

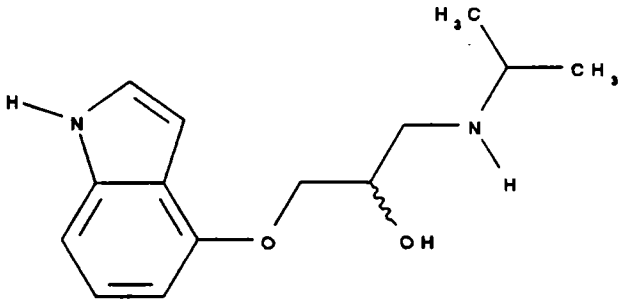
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg, 10 mg.

15. CHEMICAL NAME AND STRUCTURE

Pindolol USP, $C_{14}H_{20}N_2O_2$; M.W. = 248.32



1-(Indol-4-yloxy)-3-(isopropylamino)-2-propanol.
CAS [13523-86-9]

16. RECORDS AND REPORTS
- Method validation of ANDA 74-123 was found acceptable on January 25, 1993 by Philadelphia District, HFR-MA100.
- December 15, 1992 dated memorandum from Investigation & Compliance Evaluation Branch, HFD-324 to withold approval of application.
- October 25, 1994 dated memorandum from Investigation & Compliance Evaluation Branch, HFD-322 to withold approval of application.

17. COMMENTS
This application is satisfactory from a chemistry stand point. We called the Firm on 11-1-96 to certify and/or commit to the followings: 1) The chemistry, manufacturing and control section of their aplication has not changed related submission dated 4/24/94. 2) They certify that they will only market scored tablets. 3) They commit to updating all testing methods in their ANDA in accordance with USP 23/NF 18 as appropriate and provide copies of these methods to the Agency post-approval via the first annual report.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is considered as approvable. The approval is pending an EER.

19. REVIEWER: Sema Basaran Ph.D. DATE COMPLETED: 10-11-96.
11-15-96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074123

BIOEQUIVALENCE REVIEW(S)

Pindolol Tablets
5 and 10 mg Tablets
ANDA # 74-123
Reviewer: S. P. Shrivastava
WP 74123SDW.O91

Lemmon Company
Sellersville, PA
Submission Date:
October 18, 1991
March 25, 1992
April 30, 1992

Review of an *in vivo* Bioequivalence Study, Dissolution Data and a Waiver Request

I. Objective

To assess the bioequivalence of Lemmon's pindolol 10 mg tablets with Sandoz Pharmaceutical's Visken^R 10 mg tablets (reference).

II. Background

Pindolol is a non-selective beta-adrenergic antagonist (beta blocker) with intrinsic sympathomimetic activity in the therapeutic dosage ranges. It is indicated for the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

Pindolol is rapidly and reproducibly absorbed (greater than 95%), achieving peak plasma concentrations within one hour of drug administration. The peak plasma concentrations range from 45 to 167 ng/ml following a single 20 mg dose, indicating a 4-fold intersubject variation. Upon multiple dosing, intersubject variation decreases to 2-2.5 fold. Upon repeated administration to the same subject, variation is minimal. The blood concentrations are linearly proportional to the administered dose in the range of 5-20 mg. Pindolol has a negligible first-pass effect. In man, 35-40% of the administered dose is excreted unchanged in the urine and 60-65% is metabolized, primarily to hydroxy-metabolites which are excreted as glucuronides and ethereal sulfates. The polar metabolites are excreted with a half-life of approximately 8 hours. About 6-9% of an administered intravenous dose is excreted by the bile into the feces. Pindolol is 40% bound to plasma proteins and is evenly distributed between plasma and red cells. The volume of distribution in healthy subjects is about 2 L/kg. The disposition of pindolol after oral administration is monophasic with a half-life of approximately 3-4 hours in healthy subjects or hypertensive patients with normal renal function. In elderly hypertensive patients with normal renal function, the half-life of pindolol is more variable, averaging about 7 hours. The bioavailability of pindolol is not significantly affected by co-administration of food (PDR, 1992).

In the management of hypertension, the recommended initial dose is 5 mg twice a day administered alone or in combination with other antihypertensives. The dosage may

be adjusted in increments of 10 mg per day, up to a maximum dosage of 60 mg per day. Pindolol is currently marketed as 5 and 10 mg tablets (Visken®, Sandoz Inc., East Hanover, NJ).

III. Protocol

Laboratory/Site:

Investigator(s):

IRB Approval: , Chairman, IRB; signed 11/14/90.

Study Design

This was a randomized, single-dose, two-way crossover study in 24 fasted healthy volunteers. Phase I and II were started on December 15 and December 22, 1990, respectively. Subjects # 15 and # 23 withdrew from the study and were replaced with subjects # 25 and # 26 (Add-on, Phase I, January 5, 1991; Phase II, January 12, 1991). Subject # 26 urine was found positive in drug screen, therefore, he was dismissed, and subject 27 was added (Add-on, Phase I, January 12, 1991; Phase II, January 19, 1991). Mean Age/Range: 27 Yrs; 18-39 Yrs. Mean Weight/Range: 74 kg, 63-83 kg. Washout period was one week.

Subjects fasted for at least 10 hours before and 4 hours after dosing. They were not allowed to eat or drink alcohol or caffeine containing products for 24 hours prior to dosing. Standard meals were provided at designated times and water was allowed *ad libitum*. Lunch, dinner, and snack was given at 4, 10, and 14 hours post-dosing. Two hundred and forty milliliters of beverage was included with each meal.

Restrictions, Inclusion and Exclusion Criteria

- Medications: no prescribed or OTC medications 14 days prior to initial dosing or during the study period including cold preparations, aspirin, Bufferin, Excedrin, Anacin, etc., vitamin, and antacid (magnesium and aluminum hydroxides).
- Diets: Abstain from alcohol for 48 hours prior to the study, and tea, coffee, chocolate and cola drinks for three days prior to dosing.

- Normal healthy males between 18-45 yrs of age, with ideal ± 10% body weights were selected for the study.
- Normal exclusion and inclusion criteria were used for this study.

Test Drug: A: Lemmon's pindolol tablets, 10 mg; Lot #PB146-51; Lot size dosage units; Expiration date-10/92.

Pindolol 5 mg tablets, Lot # PB146-58; Lot size units. Used for dissolution study.

Ref. Drug: B: Sandoz's Visken[R] 10 mg tablets; Lot #139 MO791, Expiration date-7/93.

IV. Assay Methodology: (Not to be released under FOI)

V. Results

Pharmacokinetic Parameters

- Pharmacokinetic parameters are given in Tables 1 and 2. The ratios of all the parameters range between 0.88 and 1.02 with/without subjects 25 and 27.
- The 90% CIs for AUC_{0-t}, AUC_{0-inf}, and C_{max} were within acceptable limits of 80-120%.
- None of the parameters showed any significant treatment or sequence effect.
- The estimation of AUC_{inf} values for each subject (with or without subjects 25 and 27) was appropriate.
- The AUC_{0-t}/AUC_{inf} ratios for means and each subject ranged between 0.86-0.96, both for the test and reference products, with or without subjects 25 and 27 (Table 3).
- Data for subjects 5, 9 and 19 were used to check K_{el}, terminal half-life, correlation coefficient, and AUC_{0-t}. The values were comparable (Table 4).

Table 1. Pharmacokinetic Parameters (n=24)

Parameter	Test (CV)	Reference (CV)	Ratio, T/R	90% CI
$AUC_{0\text{-}T\ (last)}$, ng.Hr/mL	228.5 (32.4)	229.4 (30.7)	1.00	95.7-103.6
$AUC_{0\text{-}Inf}$, ng.Hr/mL	246.8 (32.3)	246.6 (31.0)	1.00	95.8-104.3
C_{max}, ng/mL	39.7 (24.9)	39.0 (24.5)	1.02	96.8-106.9
T_{max}, Hr	1.26 (34.9)	1.44 (33.3)	0.88	
$T_{1/2}$, Hr	3.45 (19.4)	3.49 (20.9)	0.99	
K_{el}, Hr^{-1}	0.208 (17.8)	0.207 (19.8)	1.00	

Table 2. Pharmacokinetic Parameters (n=22)
(Excluding Subjects #25 and #27)

Parameter	Test (CV)	Reference (CV)	Ratio, T/R	90% CI
$AUC_{0\text{-}T\ (last)}$, ng.Hr/mL	227.3 (33.7)	228.4 (30.7)	1.00	95.4-103.7
$AUC_{0\text{-}Inf}$, ng.Hr/Ml	245.3 (33.5)	245.3 (30.8)	1.00	95.6-104.5
C_{max}, ng/mL	39.8 (26.0)	39.2 (25.1)	1.02	96.3-107.0
T_{max}, Hr	1.26 (35.6)	1.43 (33.4)	0.88	
$T_{1/2}$, Hr	3.43 (19.5)	3.49 (20.3)	0.98	
K_{el}, Hr^{-1}	0.208 (17.4)	0.206 (19.2)	1.01	

TABLE 3: INDIVIDUAL PHARMACOKINETIC PARAMETERS AND THEIR RATIOS

SUBJ	AUCT-T	AUCT-R	AUCT T/R	AUCI-T	AUCI-R	AUCI T/R	AUCT-T/ AUCI-T	AUCT-R/ AUCI-R	CMAX-T	CMAX-R	CMAX T/R
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
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AVE	228.52	229.35	1.00	246.75	246.59	1.01	0.93	0.93	39.69	38.97	1.03

Table 4. Comparison of Submitted Pharmacokinetic Data with PKCALC Values for Selected Subjects (Two Exponentials; Unit same as in Table 2)

Subject	K_e Submitd	K_e Computd	AUC_{0-t} Submitd	AUC_{0-t} Computd	$T_{1/2}$ Submitd	$T_{1/2}$ Comptd
5-Test	0.177	0.148	319.2	319.2	3.9	4.7
5-Ref	0.166	0.184	258.3	255.7	4.2	3.8
9-Test	0.255	0.252	166.2	164.2	2.7	2.8
9-Ref	0.257	0.244	172.7	170.2	2.7	2.8
19-Test	0.227	0.229	221.0	221.0	3.1	3.0
19-Ref	0.219	0.228	235.5	223.3	3.2	3.0

Blood/Plasma/Serum: See Tables 5 and 6.

TABLE 5. Mean Plasma Pindolol Concentration at each Sampling Time Point (n = 24)

TIME (HR)	LEMMON	CV (%)	SANDOZ	CV (%)	Ratio,T/R
Pre-dose	0.00	-	0.00	-	-
0.33	14.1	82.3	12.8	81.5	1.10
0.67	33.3	37.0	29.1	41.8	1.14
1.00	36.6	26.2	34.5	25.9	1.06
1.33	36.2	23.8	35.6	23.1	1.02
1.67	36.5	22.3	36.5	26.7	1.00
2.0	35.2	22.6	35.4	27.0	0.99
2.5	32.3	25.1	33.0	26.6	0.98
3.0	29.9	26.8	30.1	25.5	0.90
4.0	25.2	29.7	25.1	26.8	1.00
5.0	21.1	32.3	21.1	30.2	1.00
6.0	16.6	36.1	16.7	32.5	0.99
8.0	11.4	39.0	11.6	36.48	0.98
10.0	7.3	42.5	7.8	41.5	0.94
12.0	4.7	50.0	4.7	49.6	1.00
16.0	1.8	119.9	2.1	95.8	0.86

TABLE 6. Mean Plasma Pindolol Concentration at each Sampling Time Point. Excluding Subjects #25 and #27 (n = 22)

TIME (HR)	LEMMON	CV (%)	SANDOZ	CV (%)	Ratio.T/R
Pre-dose	0.00	-	0.00	-	-
0.33	14.4	83.7	13.4	78.8	1.07
0.67	33.7	38.1	29.6	41.9	1.14
1.00	36.6	27.3	34.5	26.2	1.06
1.33	36.4	24.5	35.6	23.8	1.02
1.67	36.5	23.2	36.6	27.5	1.00
2.0	35.1	23.6	35.3	27.9	0.99
2.5	32.2	26.3	33.1	27.3	0.97
3.0	29.7	28.1	30.1	26.4	0.99
4.0	25.0	30.9	25.0	26.6	1.00
5.0	20.9	33.7	20.9	30.4	1.00
6.0	16.5	37.6	16.5	32.8	1.00
8.0	11.2	40.3	11.5	36.3	0.97
10.0	7.2	43.9	7.7	40.6	0.94
12.0	4.7	50.5	4.6	48.7	1.02
16.0	1.8	121.9	2.1	94.5	0.86

Adverse Reactions: No adverse reactions were reported by the subjects during the study.

VI. Formulation Composition: See Table 7 below.

Table 7. The Composition of 5 and 10 mg Tablets

Ingredients	Amount Per Tablet (mg) 10 mg	5 mg
Pindolol, USP	10	5
Microcrystalline cellulose, NF		
Pregelatinized starch, NF		
Colloidal silicone dioxide		
Magnesium stearate, NF		

Generic Name: Pindolol Firm: Lemmon Co.
ANDA #: 74-123 Submission Date: October 10, 1991

TABLE 8. *In Vitro* Dissolution Testing

Conditions

USP XXII Method, Paddle RPM: 50 No. of Units: 12
Medium: 0.1 N HCl Volume: 500 Temp: 37°C
Reference Drug: Visken® Manufacturer: Sandoz Pharm
Assay Methodology:

Results

Sampling Time (Min.)	Test Product Lot No.: PB 146-58 Strength (mg): 5			Reference Product Lot No.: 198MO619 Strength (mg): 5		
	Mean % Dissol	Range	CV	Mean % Dissol	Range	C
5	101.0		1.9	93.0		4.
10	101.0		1.8	93.0		2
15	101.1		1.8	94.0		2.
20	101.0		1.6	95.0		1.
	Lot No. PB 145-51 Strength (mg): 10			Lot No. 139MO791 Strength (mg): 10		
5	101.0		1.5	99.0		1.
10	101.0		1.4	99.0		1.
15	101.0		1.4	98.0		1.
20	101.0		2.6	99.0		1.

VII. Comments

1. The innovator labeling indicates that bioavailability is not significantly affected by co-administration of pindolol with food. In future, such labeling must be substantiated by a limited food study. The food study is conducted with at least 12 subjects in a three-way crossover (fed test and reference products with standard breakfast, and fasted test product).

VIII. Recommendations

1. The single dose bioequivalence study conducted by Lemmon Co., Inc. on pindolol 10 mg tablets, Lot # PB146-51, comparing it to Sandoz's Visken® tablets 10 mg, Lot # 139 MO791, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Lemmon's 10 mg tablets are bioequivalent to the reference product, Visken® 10 mg tablets, manufactured by Sandoz.

The dissolution testing conducted by [illegible] on its pindolol Tablets, Lot # PB146-58 and PB146-51, respectively, is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study on the 10 mg strength of the test product. The formulation of the 5 mg strength tablets is proportionally similar to that of the 10 mg strength tablets of the test product, which underwent biostudy. The firm's pindolol 5 mg tablets, therefore, are deemed bioequivalent to Visken[R] 5 mg tablets, manufactured by Sandoz. The Division of Bioequivalence recommends that the request for waiver of *in vivo* bioeqivalence study requirements for the firm's pindolol, 5 mg tablets, be granted.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should be conducted in 500 mL of 0.1 N HCl at 37 °C using USP XXII Apparatus II (Paddle) at 50 RPM. The test drug products should meet the following specifications:

   Not less than of the labeled amount of pindolol in the dosage form is dissolved in 15 minutes.

4. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements, and the application is acceptable.

The firm should be informed of the comments and recommendations.

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK ____ _____ Date 3/2/93

Concur: _____ for Date: 3/22/93

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

SPS/sps/10-18-91/74123SDW.O91

cc: ANDA #74-123, HFD-630, HFD 130 (J Allen), HFD-604 (Hare), HFD-655 (Patnaik, Shrivastava), HFD-340, Drug File.